Docket No.: 146392002400
Client Reference: P1824R1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Iqbal GREWAL

Application No.: 10/099,818 | Confirmation No.: 2744

Filed: March 14, 2002 | Art Unit: 1644

For: COMBINATION THERAPY FOR TREATMENT OF A DISORDER CHARACTERIZED BY CELLS EXPRESSING THE CD40 SURFACE ANTIGEN (AS AMENDED) | Examiner: P. Gambel

DECLARATION UNDER 37 C.F.R. 1.132

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Timothy S. Lewis, Ph.D., declare as follows:

1. I am Principal Scientist at Seattle Genetics, Inc. I have investigated the mechanism of action of dacetuzumab, an anti-CD40 antibody, in non-Hodgkin lymphoma and multiple myeloma for the past three years, including studies on combination therapies with dacetuzumab and other drugs. A copy of my CV is attached.

2. Seattle Genetics, Inc., has licensed its anti-CD40 antibody technology to Genentech, Inc., under a collaboration agreement. I am the lead scientist on the CD40 antibody collaboration at Seattle Genetics.

3. I have reviewed the specification of the above-referenced patent application and the Office Action dated April 3, 2009.

4. Although it was known in the cancer therapy field that different anti-cancer therapy might be combined for cancer treatment, it was not predictable in 2001 whether an anti-CD20 antibody and an anti-CD40 antibody combination treatment could achieve at least an additive effect for treating a cancer. Combination therapy with an anti-CD20 antibody and an anti-CD40 antibody might achieve an antagonistic effect, no significant improvement, an additive effect, or a synergistic effect, as compared to the corresponding monotherapy, when the optimized of each single agent treatment was used.

5. To test if the efficacy of a CD20-specific antibody could be improved by simultaneously targeting CD40 with a CD40-specific antibody, the anti-tumor activity of rituximab (a CD20-specific antibody) and dacetuzumab (a humanized anti-CD40 antibody) as single agents or in combination was examined in the subcutaneous Ramos (Burkitt's lymphoma) xenograft model. The studies described below were carried out by myself and by others under my supervision. Dacetuzumab is a humanized antibody derived from antibody S2C6 described in the above-referenced patent application. Like antibody S2C6, dacetuzumab binds and stimulates CD40 and enhances the interaction between CD40 and CD40L.

6. SCID mice were subcutaneously implanted with $5x10^6$ Ramos lymphoma cells and dosed when average tumor volume reached 100 mm^3 (n = 10 mice/group). Dacetuzumab and rituximab were dosed at 4 mg/kg or 8 mg/kg in the Ramos model (3 times weekly (mwf) for 3 weeks; ip) as single agents or in combination. Tumor growth progression was analyzed using a Kaplan-Meier plot generated in Prism (GraphPad Software).

7. Tumor growth was plotted as percent of mice in each group with <1,000 mm^3 tumor volume using a Kaplan-Meier plot as shown in Exhibit A. The data in Exhibit A indicate that there was no significant increase of the anti-tumor efficacy when the dosing level was increased from 4 mg/kg to 8 mg/kg by rituximab or by dacetuzumab. The median time to reach the 1,000 mm^3 tumor

volume was 58.7 days for dacetuzumab at both 4 mg/kg and 8 mg/kg dosing level, and 34.1 days for rituximab at both 4 mg/kg and 8 mg/kg dosing level. This suggests that the increase of the dosage from 4 mg/kg to 8 mg/kg did not increase the efficacy of rituximab or dacetuzumab. Thus, the 4 mg/kg dosing level is considered optimized dosing level for each antibody in this model.

8. The combined activity of dacetuzumab and rituximab (4 mg/kg each) was significantly greater than that of dacetuzumab and rituximab alone at the 8 mg/kg dosing level (P-value of 0.0041 and 0.0021, respectively). The median time to reach the 1,000 mm^3 tumor volume 58.7 days for dacetuzumab (8 mg/kg), 34.1 days for rituximab (8 mg/kg), and >100 days for the dacetuzumab plus rituximab combination (4 mg/kg each). Furthermore, the *in vivo* activity of the dacetuzumab-rituximab combination appears to be greater than additive. This study demonstrated that dacetuzumab is capable of improving the *in vivo* efficacy of rituximab.

9. Since the 4 mg/kg dosing level was optimized for each antibody, one skilled in the art would not consider that the additional benefit that was observed in the combination therapy, as compared to the monotherapy, was contributed by the increase of the total antibody dose in the combination therapy. Therefore, the additional benefit observed in the combination therapy with the anti-CD20 antibody and the anti-CD40 was not predictable or expected by one skilled in the art in 2001.

10. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

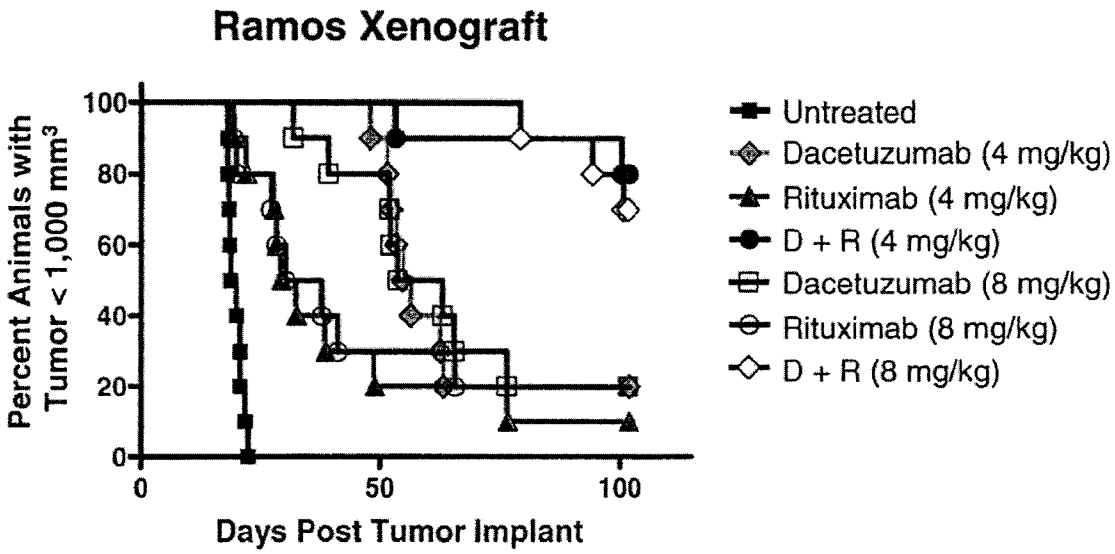
Respectfully submitted,

Dated: September 25, 2009

By: Timothy S. Lewis

Timothy S. Lewis

EXHIBIT A


Ramos Xenograft
Percent Animals with Tumor < 1,000 mm³
100
80
60
40
20
0
0
50
100
Days Post Tumor Implant
Untreated
Dacetuzumab (4 mg/kg)
Rituximab (4 mg/kg)
D + R (4 mg/kg)
Dacetuzumab (8 mg/kg)
Rituximab (8 mg/kg)
D + R (8 mg/kg)